more often observed in myelocytic than in lymphocytic types. General data on the number of cases studied and the incidence of rheumatic complaints in these cases are presented. It is concluded that pain is particularly prominent in multiple myeloma and Hodgkin's disease, and that lumbar or dorsolumbar segments of the spine are the most commonly affected. Pain occurs frequently at the onset of acute leukæmia and multiple myeloma.

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RÉSUMÉ

Parmi l'extrême polymorphisme de ces affections, les manifestations ostéo-articulaires et particulièrement vertébrales méritent une place importante tant par leur fréquence que par les erreurs diagnostiques qu'elles entraînent. Il ne fait pas de toute que, dans nos cliniques de rhumatologie, des malades se présentent et se plaignent qui devraient être explorés complètement en vue de dépister une hémopathie de ce groupe.

Le but de ce travail est d'attirer l'attention sur la fréquence des douleurs rhumatismales comme mode de début ou durant l'évolution de ces maladies.

Après avoir défini la douleur rhumatismale dans le présent travail, nous avons revu un grand nombre de dossiers de maladie de Hodgkin, lympho- et réticulosarcomes, leucémies aiguës ou chroniques et myélome multiple. Le diagnostic a été sévèrement contrôlé par les données cliniques et confirmé par un examen anatomo-pathologique: biopsie, ponction médullaire ou autopsie.

Il n'existe pas de parallélisme obligatoire entre les manifestations algiques et les lésions osseuses radiologiques. La colonne vertébrale est fréquemment touchée dans la maladie de Hodgkin et particulièrement la colonne lombaire.

L'atteinte de la colonne lombaire ou des articulations sacroiliaques donne lieu à peu près toujours à des lombalgies avec ou sans irradiation dans les membres inférieurs. Les manifestations ostéo-articulaires sont plus fréquentes dans la leucose aiguë de l'enfance que dans les autres variétés de leucémie et peuvent en imposer pour un rhumatisme articulaire aigu ou une maladie de Chauffard-Still.

Enfin, le myélome multiple peut se présenter sous un aspect rhumatismal et l'on doit toujours considérer cette possibilité devant un adulte souffrant d'altérations osseuses douloureuses que ne font pas leur preuve. La douleur rhumatismale est parmi les troubles les plus fréquents de cette affection et peut même constituer à elle seule le tableau clinique.

CLINICAL INVESTIGATION OF SUVREN—A NEW SEDATIVE PREPARATION*

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THE EFFECTS of para-butylmercaptobenzhydryl betadimethyl aminoethyl sulfide (HCl) (Covatin, N 68, Suvren, AY 55074), a new sedative agent, were studied in a group of 38 patients from January 1956 to January 1957.

Weidmann and Petersen[8] had investigated the pharmacology of 35 compounds closely related to the diphenhydramine antihistamine series in 1953. In 1955 the same investigators[9] reported on the pharmacology of the compound considered the most promising of the 35 from the point of view of sedative action. This compound, called Suvren* in Canada, is the subject of this paper.

This agent is reported to have few antihistamine effects. It is reported to be a very safe compound in terms of animal toxicity. It does not potentiate the actions of barbiturates and other hypnotics, nor does it possess any hypnotic effects. It does not cause hypotension. It is a potent spasmolytic, acting directly on smooth muscle. This effect is quantitatively four or five times greater than that of papaverine. This relaxant effect on smooth muscle is mainly on the muscles of the bronchi, gastro-intestinal tract, ureters, biliary system, and blood vessels.[9]

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This drug had no hypnotic effect. The "sedative effect" was experimentally defined as the reduction of spontaneous activity of small animals, generally mice or rats. On pharmacological study it was felt that this agent possessed the ability to modify energy output as measured by spontaneous activity.

The manufacturers felt that this agent should be tested for its ability to allay activity and excitement, to calm, and to reduce irritability. These properties were defined as its sedative effect. Its clinical investigation as a mild daytime sedative was therefore recommended, and it was also studied as an adjuvant in the treatment of certain of the severer psychiatric conditions. It was not thought to be indicated for symptomatic treatment of acutely agitated patients, or for the more severe psychiatric states.

RESEARCH DESIGN

Thirty-eight patients were studied over a year, from January 1956 to January 1957. They consisted of two main groups:

Group I: Eighteen inpatients with marked disorders of affect were selected irrespective of diagnosis. This group was studied along the lines described in our previous publications on drugs in psychiatry.[3-7] Briefly, patients with gross disorders of affect are given psychotherapy, the drug being the only external variable added. The physiological effects of the drug tested are determined, screening tests for toxicity are done, and the way in which these effects modify the expression of emotion is observed. Knowledge of the psychodynamic, interpersonal, and milieu factors is used to help evaluate the results.

In terms of the claims made by the manufacturers, this was a most severe test. The authors nevertheless felt that it would still be worth while to test this drug in this way, as well as to have a second group of patients to whom it would be given as a sedative.

Group II: This group was selected irrespective of diagnosis from patients who needed a mild daytime sedative. This group consisted of 13 patients in a psychiatric day hospital (Jewish General Hospital) as well as a group of 7 selected patients given psychotherapy in office practice. All patients were selected on the basis of being followed closely enough in psychotherapy for some opinion to be offered on the relative effects of psychotherapy and of the drug; any effect which could be attributed to psychotherapy was not attributed to the drug.

TABLE I.—DIAGNOSIS IN 38 CASES

Group I.		*Total*
Schizophrenia:		5
Chronic undifferentiated	1	
Paranoid	4	
Anxiety reaction:		6
Anxiety reaction	4	
Anxiety reaction in a passive-dependent personality	2	
Depressive reaction:		7
Depressive reaction	2	
Depression in an obsessive-compulsive	1	
Depression with agitation	2	
Depression with strong paranoid trends (in the 4th to 6th decade)	2	
		18
Group II.		*Total*
Anxiety reaction:		6
Anxiety reaction	4	
Anxiety reaction in a passive-dependent personality	2	
Phobic reaction		1
Conversion reaction		1
Dissociated reaction		1
Manic		1
Depressive reaction:		10
Depressive reaction	3	
Depression in a high-grade mental defective	1	
Depression in an obsessive-compulsive personality	2	
Chronic depression (>1 year)	4	
		20

Data.—Twenty-three of the patients were male and 15 were female; 9 were in the second decade, 11 were in the third, 10 were in the fourth, 6 were in the fifth, 1 was in the sixth, and 1 in the seventh. Table I shows the diagnostic categories.

Dose.—All medication was given in 50 mg. pills per os in divided doses three or four times a day. All patients in Group I received 150 to 400 mg. per day. One patient received 400, 3 received 200, 7 received 300 mg. Duration of treatment in Group I varied from 2 to 44 days.

In eight patients the drug was discontinued after 2 to 12 days. This occurred in some for reasons concerned with the patient's reactions in terms of transference. In others, it was motivated by the severe nature of their illness, and the need for other treatment (see Table II). Ten patients were treated for 12 to 44 days.

The 20 patients in Group II received 150 to 500 mg. per day. One received 500, 2 received 400, 5 received 200, 11 received 300 mg. Seven patients were treated for 3 to 12 days. Table II shows the reason for discontinuing the drug during this period. One patient was treated for 170 days, and the rest for 12 to 150 days.

TABLE II.—CASES ON DRUG ONLY 2 - 12 DAYS (14 PATIENTS)

Group I.	*Total*
Discontinued because patient panicked (transference phenomenon) After 12 days—disturbed because of "metallic taste".	1
Discontinued because of conjunctivitis:* (not caused by drug but at the time this was not certain) After 8 days.	1
Patients too ill, needed other treatment (E.C.T., commitment, etc.)*	5
Improved and ran away from transference: (equivalent to panic) After 8 days. Recovered from post-alcoholic depression.	1
	8
Group II.	*Total*
Panicked while on drug (transference phenomenon)† All after 3 to 5 days.	3
Patients too ill, became worse, or needed other treatment* 1 patient became hypomanic. 1 patient needed E.C.T.	2
Didn't take medication regularly because of transference distortions of physician's motives	1
	6

*In some of these patients, there was nevertheless evidence for a sedative effect. The total course of the illness, however, determined the change in treatment.

†One of these patients had also received chlorpromazine, bromides, and phenobarbital on other occasions, and had panicked equally on all of them.

There were no significant changes in blood pressure, pulse, respiration, or weight. Our routine for attempting to measure the observable physiological effects was that described in our previous publication.[3]

SIDE-EFFECTS AND TOXICITY

There were no truly toxic reactions in this series. No biochemical toxicity was shown. Three patients complained of a "metallic taste" in their mouths. This occurred one to two hours after the ingestion of the drug, and persisted for at least four to six hours. All of these patients were receiving at least 300 mg. per day. One of these also complained of a "dry mouth". Three other patients complained of "dry mouth" without the "metallic taste". Two patients complained of a "bitter taste" occurring one to two hours after ingestion and persisting for several hours. These patients received 300 mg. per day. The authors assumed that this was identical with the "metallic taste" complained of by the other two patients.

Thus, three patients complained of "metallic taste" and two more of "bitter taste," giving a total of five with this complaint. Three others complained of "dry mouth." Several other patients had varying degrees of this, but did not really suffer from this effect.

One patient complained of nausea, but he had entered hospital with this complaint, and its severity varied with the intensity of his emotional turmoil rather than with the drug ingestion. Another patient complained of marked anxiety and "cardiac distress," with no objective signs of cardiac disorder, whenever he took his pills. This was considered a transference anxiety reaction.

Thus, side-effects and toxicity were low in this series.

RESULTS

Results were classified in two ways. (1) Was there evidence for the sedative activity of the agent? Slowing of motor activity, increased feelings of tiredness, and side-effects were looked

TABLE III.—SEDATIVE EFFECTS OF SUVREN—38 CASES

	Group I	*Group II*	*Total*
More "objective" evidence for sedative effect: diminished energy output, increased ability to sleep, dry mouth, metallic taste, as well as the subjective effects such as feeling calmed, more tired, less irritable, less tense	10*	5*	15
Evidence of sedative activity present, but inseparable from purely subjective feelings or from results produced by transference (i.e., sedative effect due to patient's feeling that a strong, powerful and benevolent physician was helping him with a "good pill"). This result is sometimes obtainable without any drug being administered. Interpretation open to question, yet it was nevertheless felt that the drug did have some effect in these cases	4*	10*	14
No evidence for sedative activity	4	5†	9
			38

*In some of these cases treatment results were poor in terms of the outcome of psychotherapy while patient was receiving the drug. There was nevertheless evidence for the drug's sedative effect in these cases, even though the treatment result was poor. This was due to varying factors: severity of illness, negative transference, need for other treatment such as E.C.T.

†Some of these cases could not adequately be evaluated for sedation because of the rapidity with which symptoms increased, especially in terms of anxiety, panic, or conversion symptoms. These were negative transference phenomena and had to do with the personalized psychological meaning of taking the "doctor's pill". We have previously referred to this phenomenon.[4-7] The remaining cases were just too ill.

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for, as well as the patient's subjective feelings of being calmed and feeling less tense. The limitations that transference and other psychotherapeutic effects imposed on the evaluation of the drug's sedative action were very apparent, and are discussed later. This highlights the difficulty in obtaining objective criteria for the evaluation of a mild sedative preparation—especially one without hypnotic activity.

(2) The final outcome of treatment while on the drug was also gauged, but merely to offer some criteria of what happened to the patient while on psychotherapy and the drug. These latter results, called treatment results, were not primarily based on the action of Suvren, but show the disposal of the patients at the time the drug was discontinued, in total terms of what psychotherapy and the sedative had produced (see Table IV).

TABLE IV.—TREATMENT RESULTS (PSYCHOTHERAPY + SEDATIVE)*

	Group I	*Group II*	*Total*
POOR RESULTS			
Committed, or given E.C.T., or other organic treatment..	2	1	3
Placed on other treatment or other medication.....	2	2	4
Panicked and/or ran away from treatment.....	3	5	8
Total.....			15
GOOD RESULTS			
Psychotherapy plus sedative permitted patients' symptoms to diminish during treatment period.....	11	12	23
Total.....			23

*These results are *not* due to the drug alone, but show the disposal of patients at the time the drug was discontinued.

No change was classified as a poor result.

Three patients in day hospital were not initially used in the study because they had received Suvren along with electric shock. In these cases the observers had felt that the results of the treatment were good, but the role of the sedative was not clear. Two patients in day hospital who received sub-coma insulin were not used for similar reasons. All five patients were charted in the study after these treatments had been stopped, a base line established, psychotherapy continued, and Suvren added as a sedative.

It is interesting to note that several patients who initially complained of insomnia when placed on Suvren (especially when night-time hypnotics were discontinued because of our research design) were able to sleep with no night-time sedation after the first week of medication. In these cases this was used as evidence for sedative effect, since it indicated a general lessening in the level of anxiety. Here again, in some it was impossible to separate the influence of transference from those factors due to the drug. Table III shows the evidence for positive sedative action, while Table IV shows the eventual outcome of treatment.

The manufacturers' statement that this drug was not indicated for modification of emotions or behaviour of extremely agitated or disturbed patients was borne out. Pharmacologically, this agent was not powerful enough, at least in the recommended doses used, to significantly modify behaviour.

It is significant, however, that in this series evidence for sedative effect was shown in 29 of the 38 patients (see Table III). It often proved impossible to separate the influence of the sedative action from the feelings of well-being produced by psychotherapy, and the rapid establishment of a transference, as well as the protective and reassuring hospital milieu (14 of the above 29 patients—see Table III).

DISCUSSION

The difficulties of properly evaluating a mild sedative preparation are highlighted by this study (see Table III). It is most important in studying drugs in psychiatry to look for clear-cut physiological effects. When these can be measured, it is then important to attempt to evaluate the psychodynamic, interpersonal, milieu, and nonspecific factors involved in the process of recovering from psychiatric symptoms while under psychotherapy. This latter enables one to differentiate between the effects of transference and the physiological effects of the drug. The two may be synergistic. The fact that the mere ingestion of a medication is often incorporated in the patient's transference is a point of very considerable importance.

In this study evidence for the sedative effect, i.e., reduction of spontaneous activity, as well as a calming effect, was found in 29 of a total of 38 patients. In 14, this could not be separated

from the psychotherapeutic process in terms of cause and effect, and here it is obvious that independently of any positive sedative effect, or the absence of any sedative effect, the patient integrated the taking of the "doctor's pill" into his positive transference feelings. This is not different from what one would expect with any mild sedative (e.g., phenobarbital). One important difference existed, however, and that is the absence with Suvren of any hypnotic effects. This played an important negative role, since most patients have been conditioned to feel that a sedative also "makes you sleepy". In psychotherapy, once the patients complained of insomnia, the physiological effects of the drug in not acting as a hypnotic were pointed out.

This accents the importance of clinical investigators being aware of the influence of such factors on patients' subjective appraisal of a drug, and of the patient's acceptance or rejection of it. Patients who panicked or who ran away from treatment showed the type of transference distortions already described in our previous publications.[3-7] This is not attributable to the drug but can occur with certain patients on any medication. Table II includes those patients who presented this phenomenon.

CONCLUSIONS

Suvren has a place as an adjuvant to psychotherapy for psychiatric patients in whom a mild daytime sedative with no hypnotic effects is indicated.

It should be noted that this drug seems to show a cumulative effect, activity of the agent usually being evident by the 5th to the 7th day. In the cases studied for longer periods, our observations tend to confirm that of Arnold, who felt that the sedative effect is often delayed, and that the best sedative effect was seen after 20 days.[1] Arnold's opinion that Suvren is more suitable for the patient who needs sedation over an extended period, rather than for those who need it for only a few days, is supported by our findings. Patients who tended to do well on this agent usually liked to continue its use, there being no difficulty with those patients who used it for more extensive periods.

The general conclusions drawn from the limits of this study tended to confirm some of the opinions expressed by others:[1, 2, 10, 11] that this drug is a useful, mild daytime sedative with no appreciable hypnotic effects, no known toxicity, and relatively few and mild side-effects.

SUMMARY

Thirty-eight patients were studied for one year. The presence or absence of sedative effect was the criterion of the drug's activity. Treatment consisted of psychotherapy plus the sedative. Research design was the same as previously reported.[3-7] Treatment results were therefore not evaluated in terms of the drug alone.

This study highlights the difficulties in measuring the physiological activity of a mild sedative preparation, especially one without hypnotic effects. It is impossible in some cases to separate changes due to psychotherapy and transference from those influenced by the drug (see Table III).

In this series, 29 of the 38 patients showed evidence for sedative effect. In 14 of the 29, although the authors felt that the drug contributed to the sedative action, it proved impossible to separate this from the changes produced by psychotherapy, transference, and the protective hospital milieu.

The drug shows a cumulative effect, the first changes attributed to it being seen in five days. Others feel that optimal effects become observable between 14 and 20 days, and thereafter.[1]

In the doses used, Suvren is a useful daytime sedative with no hypnotic effects, no known toxicity, and a low incidence of mild side-effects. The authors feel that it is a useful adjuvant to psychotherapy in selected patients, especially those who may need long-term sedation.

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